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PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 010091-125	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/06111	International filing date *(day/month/year)* 10 March 2000 (10.03.2000)	Priority date *(day/month/year)* 12 March 1999 (12.03.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 49/00 and US Cl.: 424/9.1		
Applicant GEORGETOWN UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 October 2000 (12.10.2000)	10 September 2001 (10.09.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D. Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/06111

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-91 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 92-98 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-12 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-34 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-19

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9-19

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-8 and 20-33

WRITTEN OPINION

International application No.
PCT/US00/06111

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-8, 20, 21 and 23-33	YES
	Claims	22	NO
Inventive Step (IS)	Claims	33	YES
	Claims	1-8 and 20-32	NO
Industrial Applicability (IA)	Claims	1-8 and 20-33	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 21 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 22 indefinite for the following reason(s): Claim 21 refers to the method of claim 18. Claim 18 does not disclose a method, it discloses a compound. Claim 21 has been interpreted to be dependent on the method of claim 20, which is a method of inhibiting tumor invasion or matatisis using an inhibitor.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claim 22 lacks novelty under PCT Article 33(2) as being anticipated by Shi et al. (Cancer Research, 1993). A method of identifying a compound that specifically binds to a single chain or a two-chain (active) form of matriptase. The reference discloses a method of determining the inhibition of the 80 kDA protease obtained from human breast cancer cells using gel-zymography studies. In this assay, if the inhibitor does not bind to the two chain (active) form there will be no inhibition of catalytic activity. Hence, if catalytic activity is reduced or inhibited then the compound is identified to specifically bind the protease. Therefore, the instant invention is anticipated by Shi et al.

Claims 1-8, 20 and 21 lack an inventive step under PCT Article 33(3) as being obvious over Kennedy et al. (US 5,505,946) in view of Moy et al. (Cancer Letters, 1994). The instant invention is drawn to a method of treating malignancies, pre-malignant conditions and pathologic conditions, using a therapeutically effective amount of a matriptase modulating agent. The matripatase modulating agent is Bowman-Birk inhibitor (BBI). Kennedy et al. teach the use of at least 25 chymotrypsin inhibitor units BBI concentrate (BBIC) to treat pre-malignant conditions in an animal. The pre-malignant tissue is obtained from breast, colon, oral mucosa, esophageal, liver, lung, hematopoietic or prostate tissue. The tissue is obtained by biopsy (column 9, lines 29-35) and tested. Moy et al. teach using the Bowman-Birk inhibitor to treat proteolytic activity of a human breast cancer cell line. The effect of the Bowamn-Birk inhibitor on matriptase is an inherent property of the inhibitor. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the Bowman-Birk inhibitor to treat pre-malignant conditions. One having ordinary skill in the art would be motivated to utilize an inhibitor that is present in natural foods in order to treat a subject. Therefore, the instant invention is obvious over Kennedy et al (US 5,505,946) in view of Moy et al. (Cancer Letters, 1994).

Claim 23-32 an inventive step under PCT Article 33(3) as being obvious over Lin et al. (Journal of Biological Chemistry, 1997) in view of McKenzie et al. (US 5,084,266). The instant invention is drawn to a method of diagnosing malignant and pre malignant conditions in vitro and in vivo. Lin et al. teach the production of monoclonal antibodies that detect the 80 kDa protease identified from human breast cancer cells. The reference teaches using immunofluorscence to detect the distribution of the 80 kDa protease on breast cancer cells, control cells do not show any staining with these antibodies (see figure 6). McKenzie et al. teach using labeled antibodies to detect tumors in a subject (see example 3). It would have been obvious to one of ordinary skill in the art to use the antibodies of Lin et al. to evaluate needle aspiration samples in vitro for the presence of cancerous tissues of the breast. It would also have been obvious to one of ordinary skill in the art to use the antibodies of Lin et al. for the in vivo tumor imaging methods taught by McKenzie et al. One having ordinary skill in the art would have been motivated to do this in order to screen more tumor markers reduce the possibility of having a tumor go undetected. Therefore, the instant invention is obvious in view of Lin et al. in view of McKenzie et al.

Claim 33 meets the criteria set out in PCT Articles 33(2) and (3), because the prior art does not teach or fairly suggest molecular modeling to determine the compounds that specifically bind matripatse. Molecular modeling is a powerful and art established technique viewing the active site of protease. For successful modeling the requirements are that the protein sequence is determined

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

and the active site is predicted to be closes to a prior art crystal structure. The prior art discloses the crystal structure of several proteases including chymotrypsin and trypsin. The prior art does not disclose a protein or nucleotide sequence for matriptase, which is required for the molecular modeling method. Therefore, in light of prior art, the subject matter of claim 33 is novel and inventive as required by Articles 33(2) and (3).

Claims 1-8 and 20-33 have industrial applicability as set forth in PCT Article 33 (4).

---------- NEW CITATIONS ----------

MOY et al. A proteolytic activity in a human breast cancer cell line which is inhibited by the anticarcinogenic Bowman-Birk protease inhibitor. Cancer Letters. 1994, Vol. 85, pages 205-210, see table 2.

SHI et al. Identification and characterization of a novel matrix-degrading protease from hormone-dependent human breast cancer. Cancer Research. 1993, Vol. 53, pages 1409-1415, see figure 7.